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Review

Huntington's disease: An update of therapeutic strategies

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ABSTRACT

Huntington's disease (HD) is an autosomal dominant triplet repeat genetic disease, which results in progressive neuronal degeneration in the neostriatum and neocortex, and associated functional impairments in motor, cognitive, and psychiatric domains. Although the genetic mutation caused by abnormal CAG expansion within the *htt* gene on chromosome 4p16.3 is identified, the mechanism by which this leads to neuronal cell death and the question of why striatal neurones are targeted both remain unknown. Patients manifest a typical phenotype of sporadic, rapid, involuntary control of limb movement, stiffness of limbs, impaired cognition and severe psychiatric disturbances. There have been a number of therapeutic advances in the treatment of HD, such as fetal neural transplantation, RNA interference (RNAi) and transglutaminase inhibitors (Tgasei). Although there is intensive research into HD and recent findings seem promising, effective therapeutic strategies may not be developed until the next few decades.

1. Introduction

Huntington's disease (HD) was first described by an American physician, George Huntington, in 1872 after he studied several affected individuals and also noted observations made by his father and grandfather (Neylan, 2003). It is an adult-onset, chronic and progressive neurodegenerative disease and clinically characterized by abnormal choreic involuntary movements and by psychiatric, psychological and intellectual disorders, and radiologically characterized by striatal atrophy of variable degree. Pathologically, in atrophied striatum, the normally predominant small projecting neurons are specifically affected. Since these neurons are inhibitory in function, their long axons terminate in the substantia nigra and use γ-aminobutyric acid (GABA) as a neurotransmitter and these GABA levels in the substantia nigra of HD are markedly low (Perry et al., 1973). On the other hand, dopaminergic nigral neurons remain intact in HD and the dopamine level in the HD striatum is higher than normal (Spokes, 1980). Therefore, HD is regarded as a relatively dopamine-predominant disease. In agreement with this finding, anti-dopaminergic drugs are clinically effective against choreic movements.

2. Genetic insight and molecular biology of the disease

HD is a single gene disease with autosomal dominant inheritance pattern and prevalence is about 5 in 100,000 worldwide (Clarke, 2005). Penetrance is almost 100% as individuals with the dominant allele eventually develop the disease. The average age of onset is 38 years, though the timing ranges from 25 to 70 years. However, approximately 5% of HD cases have presented before 20 years of age (Turnpenny and Ellard, 2007). Although the disease locus of HD was mapped to chromosome 4p16.3 by the G8 marker in the early 1980s, the HD gene was not cloned until 1993 (Gelehrter et al., 1998). HD is caused by the mutation of the gene IT15, which contains 67 exons and encodes a 3144-amino-acid protein called "huntingtin (htt)" (Young, 2005). The function of htt is unclear. It is essential for development and that absence of htt is lethal in mice (Nasir et al., 1995). HD gene is essential for post-implantation development and that it may play a significant role in the normal functioning of the basal ganglia. The wild-type htt up-regulates the expression of Brain Derived Neurotrophic Factor (BDNF) at the transcription level; however, the mechanism by which huntingtin regulates gene expression has not been determined (Zuccato et al., 2001).

The normal and intermediate alleles have 10–26 and 27–35 CAG repeat respectively. Individuals with more than 39 CAG repeat will almost

Abbreviations: HD, Huntington's disease; htt gene, huntingtin gene; HDACi, histone deacetylase inhibitors; RNAi, RNA interference; ASO, antisense oligonucleotide; Tgasei, transglutaminase inhibitors.

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always show manifestations of HD (Mueller and Young, 2001), with the largest expansion observed being 121 trinucleotides (Kremer et al., 1994). CAG encodes the amino acid glutamine within the htt gene on chromosome 4, and it is not toxic in itself as it is present in all humans. However, the expansion of polyglutamine tract results in aggregate formation that may become toxic and could be one of the factors responsible for HD as aggregates are never observed in the brains of unaffected individuals (Fig. 1) (Difiglia et al., 1997; Becher et al., 1998). This aggregate formation responsible for secondary complications, like apoptosis, excitotoxicity, mitochondrial dysfunction, transcriptional dysregulation, was associated with HD and was ultimately responsible for disturbed neuropathological features (Fig. 1). Approximately 70% of the variation in the age of onset of the disease is linked to the size of the CAG repeats while 13% of the variation in the onset has been attributed to polymorphism in the GRIK2 gene, whose product forms part of the subunit of the excitatory glutamate receptor (Lutz, 2007). Therefore, there are other factors that can affect the onset, severity, and outcome of HD.

3. Current management and therapeutics

At this time, there is no cure for HD. The majority of therapeutics currently used in HD are designed to ameliorate the primary symptomatology of the HD condition itself (psychiatric agents for the control of behavioral symptoms, motor sedatives, cognitive enhancers, and neuroprotective agents) and thus and improve the quality of life of the patients (Handley et al., 2006a, 2006b). It is important to determine whether patients require treatment when they present. In the early stages, the chorea may not be interfering with their lifestyle and so may not require treatment. However, if the symptoms begin to affect their lifestyle such as in walking, writing and eating, then intervention becomes a necessity. The neuronal dysfunction and cell death in HD are due to a combination of interrelated pathogenic processes. Many of the compounds are being tested in cell culture and in different animal models of the disease.

Currently, there are several potential therapeutic agents (memantine, tetrabenazine, minocycline, treahalose, C2–8, creatine, coenzyme Q10, ethyl-EPA, cysteamine, HDAC inhibitors, mitramicycin) mostly acting on the above-mentioned downstream targets that have shown improvement of motor and/or cognitive dysfunction mostly in the R6/2 and N171-82Q mouse lines. Up to now, seven compounds have been systematically tested in HD patients at different stages of the disease. Currently, these compounds are in phase II (creatine, coenzyme Q10) and in phase I (minocycline, cysteamine, memantine, ethyl-EPA) (Table 1). Here, we will discuss the HD therapeutics currently under development focusing on their benefits and limitations.

3.1. Drugs against excitotoxicity

Excitotoxicity is one of the major causes of cell death in HD. Excitotoxicity relies on increased glutamate release and increased

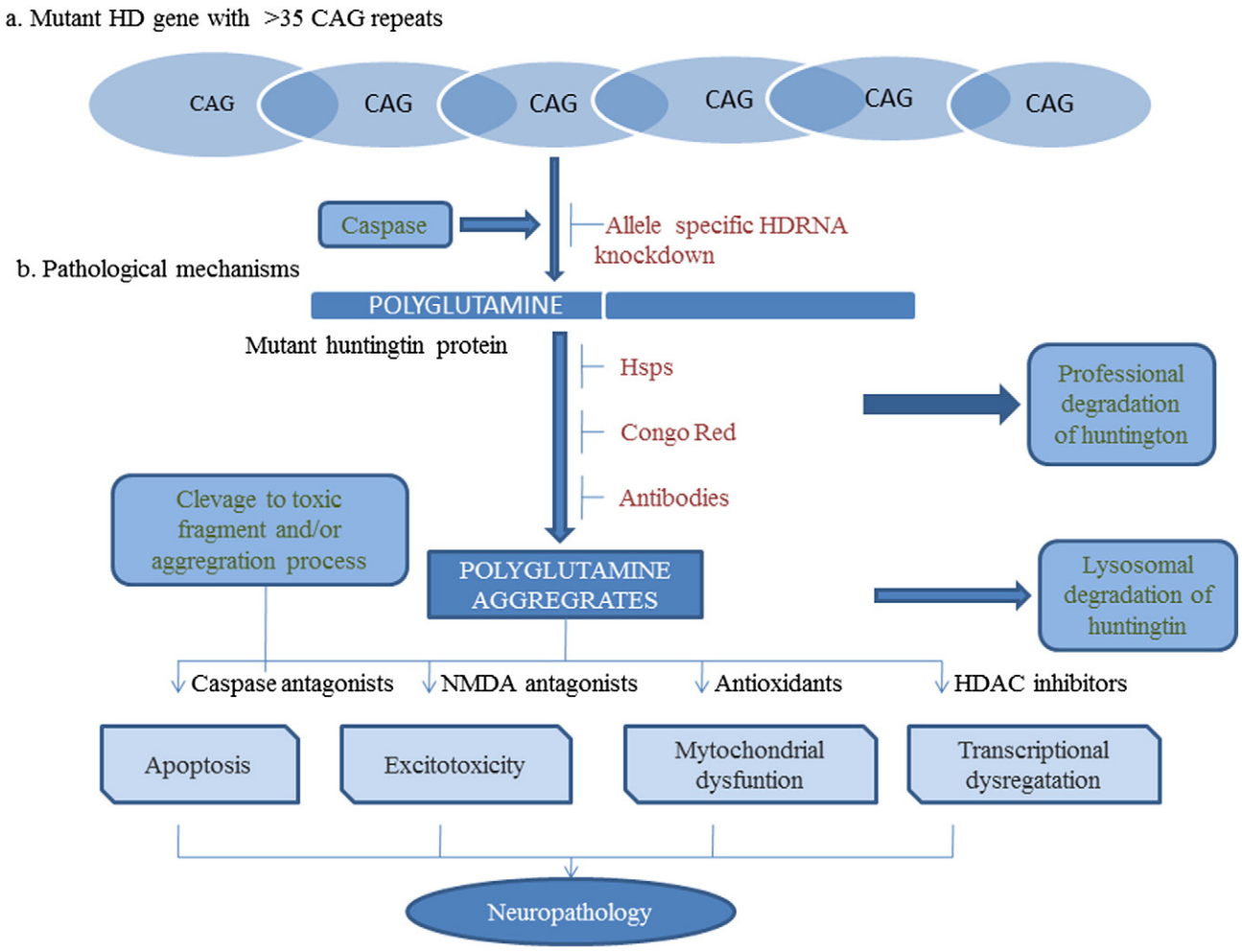

Fig. 1. Proposed mechanisms of toxicity of the HD gene and potential therapeutic targets.